PALL Medical

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July 16, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 98D-1171

Dear Sir or Madam:

Medsep Corporation is hereby commenting on Docket No. 98D-1171, the draft "Guidance for Industry: For Platelet Testing and Evaluation of Platelet Substitute Products". Please see our attached comments. We thank the FDA for addressing this important issue and for allowing us the opportunity to comment.

Please contact me at 626-915-8227 if you have any questions regarding this response.

Best regards,

Edward J. Nelson, RAC
Director, Regulatory and Scientific Affairs
Medsep Corporation, A Subsidiary of Pall Corp.

98D-1171

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Topic: Platelet Testing and Evaluation of Platelet Substitute Products
Comments on FDA Draft Guidance Document

INTRODUCTION

Currently, the Pall Medical Blood Processing Group Research and Development team utilizes the following general battery of *in vitro* platelet tests for pre-clinical evaluation: platelet and white blood cell counts, pH and pO_2, extent of shape change (ESC), hypotonic shock response (HSR), morphology (as %discs), glucose consumption, mean platelet volume (MPV), streaming, and lactate production. In our nearly 30 years experience of using these tests, we have been able to pre-clinically predict successful *in vivo* outcomes (%recovery and survival) in all cases except one. In this one case, the unexpectedly poor *in vivo* outcome was predicted, post-clinically, by these *in vitro* tests of the product used in the clinical trial (the preservative was not stable and had degraded).

In our laboratory, use of various other *in vitro* tests (aggregation to single agonists (ADP), β-thromboglobulin (β-TG), supernatant lactate dehydrogenase (LDH) levels, platelet factor (PF)-4 release, PF-3 activation, and the surface marker GMP-140 (p-selectin)) resulted in scant useful information when employed in paired study designs (i.e., test versus control in pooled-split experiments). These tests were found to be too sensitive, insensitive, or too variable and thus limited our ability to predict clinical success.

SPECIFIC RECOMMENDATIONS

A. *In vitro* Evaluation of Platelet Biochemistry and Function

The stated desire is to conduct a reasonable number of *in vitro* platelet tests looking at various aspects of platelet physiology. The objective being assessments comparing the new procedure or condition to current practice. The following comments are in response to the section regarding the state of platelets before and after the procedure.

Morphology:
Currently we estimate the number of discs versus non-discs (spheres, balloon and other bizarre forms) in platelet samples standardized (platelet concentrate diluted with fresh platelet free plasma) to a platelet concentration of 300/nl. The sample is incubated for 30 minutes at 37°C to allow pseudopodial retraction and reversion from spheres to discs. Regarding electron microscopy, we feel it would not provide additional useful information beyond what is currently provided by our standard *in vitro* tests.

Biochemical Status:
Glucose and lactate measurements are part of our current test regimen. ATP levels drop slightly during normal storage of platelet concentrates (PC) for five days[1], but may offer useful information. S. Holme[2] found a slight correlation comparing decreased %recovery when ATP levels in stored PC are less than 70% of day 1 PC. However, accuracy in intracellular ATP levels is questionable as some of the ATP is in non-metabolic storage pools[1]. Lactate dehydrogenase may be too insensitive in predicting *in vivo* viability but, with further study, may prove useful as a surrogate structural integrity test.

Regarding pH, we propose reporting the pH values at 22°C. With regard to pH values greater than 7.6 being detrimental, to our knowledge this was demonstrated[3] in only one particular container under certain types of agitation. We do not feel there is sufficient data to suggest this is an upper pH limit for all systems.

Platelet activation markers:
GMP-140 (p-selectin, CD62) and β-TG appear to be too sensitive as markers of platelet activation to be useful on a regular basis. Concerns about PF-3 and PF-4 test variability and sensitivity question the utility of the resulting data. Intriguing is the possible use of CD63 and the active form of GPIIb/IIIa although one major problem is the cost of obtaining a flow cytometer.

Physiologic responses:
So far ESC and HSR provide very useful information, and we recommend their use. Aggregation may be useful as a functional test (except determining *in vivo* viability). Specific agonist or agonist combinations should be defined, as the utility of some of the resulting information is questionable. Serotonin uptake or secretion and expression of activation markers are questionable due to the questions regarding the sensitivity of these tests. Further clarification of the utility of these tests (serotonin and activation markers) is warranted before specifying them as required.

Quantitation of microparticles:
Several questions arise about measuring for microparticles (MP). What type of MP? How to measure for MP? If using a particle analyzer, is the size of the MP so small that the signal-to-noise ratio would significantly impact the resolution of the results? We do not feel there would be any additional benefit gained from conducting this test.

Comments:
We agree about using paired experiments. In general, we utilize an experimental design whereby we pool PRP and subsequently divide the PRP into test and control PC units.

We are slightly confused about the comparison of non-plasma PC to plasma PC. Fresh frozen plasma (FFP) is used as the diluent in both cases to standardize the diluent matrix and to mimic the patient's circulatory environment. If we use stored platelet free plasma (PFP) from each unit excessive sampling of the stored PC would be required to produce the PFP volume necessary to perform the ESC and HSR tests. Excessive sampling would impact the surface-to-volume ratio and may severely affect (and bias) the pH, pO_2, and possibly all other measures.

B. Platelet Survival in Circulation
No comments for this section.

C. Clinical Hemostatic Efficacy
No comments for this section.

D. Evaluation of Platelet Substitutes

No comments for this section.

Evaluation of prothrombotic potential and immunogenicity:

No comments for these sections.

Additional toxicity due to platelet additives:

No comments for this section.

Comments:

We agree that a clear risk-benefit analysis must be performed prior to clinical trials. The question remains of what defines the cut-off for proceeding to clinical trials.

RECOMMENDATIONS

For simple modifications to licensed products we suggest the following tests: platelet counts, MPV, pH and pO_2, ESC and HSR, morphology (as %discs), swirling, glucose consumption and lactate production.

For major changes, such as new plastic containers or new preservative solutions, we suggest the following additional tests: *in vivo* recovery and survival. Additionally, depending upon product utility, the following tests may be appropriate: ATP, the activation markers CD63 and GPIIb/IIIa, and a test for hemostasis.

Thank you for your excellent examination of this important topic and for the opportunity to comment on the document. We hope our comments have been helpful.

Medsep Corporation

REFERENCES

1. Murphy S. Platelet storage for transfusion. Seminars in Hematology 22:165-177, 1985
2. Holme S. Storage and quality assessment of platelets. Vox Sanguinis 74 (suppl. 2):207-216, 1998
3. Murphy S., Kahn RA, Holme S., et al. Improved storage of platelets for transfusion in a new container. Blood 60:194-200, 1982

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